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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/835,126

Filing Date: April 16, 2001

Appellant(s): NOELLE ET AL.

**MAILED
JAN 11 2007
GROUP 1600**

**Chandra Garry
For Appellant**

EXAMINER'S ANSWER

This is in response to the Appeal Brief, filed October 3, 2006, appealing from the Final Office Action, mailed December 30, 2005 and in accordance with the Pre-Appeal Conference Pilot Program, wherein the Panel Decision from Pre-Appeal Brief Review was mailed August, 3, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the Brief.

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(2) Related Appeals and Interferences

Related USSN 09/951,537 is currently under appeal from a Final Office Action, mailed December 30, 2005 and in accordance with the from a Panel Decision from Pre-Appeal Brief Review dated August, 3, 2006.

The rejections on appeal in this application are similar to those in commonly assigned USSN 09/951,537. Accordingly, the Board should consider these appeals together.

The examiner is not aware of any other related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the Brief is correct.

This appeal involves claims 1-2, 4-7, 10-11 and 13.

Claims 14-15 have been withdrawn from consideration as being drawn to non-elected species.

Claims 3, 8, 9 and 12 have been canceled previously.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the Brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

Appellant's statement of the grounds of rejection to be reviewed on appeal is correct, except for the following.

(A) Grounds of Rejection Withdrawn.

Upon reconsideration, the previous rejection under 35 USC 112, first paragraph, written description / new matter with respect to the recitation of "for a time ranging from about 5 to 30 days" recited in claim 6 has been withdrawn in view of the disclosure on page 8, paragraph 4 of the instant specification.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(8) Evidence Relied Upon

- A) Knulst et al., Eur. J. Immunol. 23 : 299-302, 1993.
- B) Noelle et al., U.S. Patent No. 5,876,718.
- C) Ochoa et al., U.S. Patent No. 5,725,855.
- D) Riddell et al., J. Immunol. Methods 128: 189-201, 1991.
- E) Rooney et al., U.S. Patent No. 5,962,318.
- F) Sykes et al., U.S. Patent No. 6,006,752.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Rejection under 35 U.S.C. § 112, first paragraph, Written Description / New Matter.

Claims 1, 2, 4-11 and 13 are rejected under 35 U.S.C. 1 § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:

- (i) "purifying CD4⁺ T cells from donor tissue" as well as steps recited in claim 1(iii)(iv)(v)(vi), as they read on "purified donor CD4⁺ T cells / T cell tolerance" AND
- (ii) "for a time ranging from 6 to 10 days" (see claim 7).

Appellant's amendment, filed 9/23/05, directed support to various sections of the instant specification, but has only relied upon Examples 1-2 and 5 described in the instant specification as-filed.

However, the specification as filed does not appear to provide sufficient written description for (i) "purifying CD4⁺ T cells from donor tissue" as well as steps recited in claim 1 (i)(iii)(iv)(v)(vi), as they read on "purified donor CD4⁺ T cells / T cell tolerance"

While the instant Examples provide observations concerning the hyporesponsiveness of isolated CD4⁺ T cells that were exposed to anti-gp39 antibodies in testing the efficacy of anti-gp39 antibodies on those gp39-expressing CD4⁺ T cells under those particular conditions and purposes and not on purification and administration of purified CD4⁺ T cells to a recipient in need of transplantation (e.g., see claims 1, 10 and 11).

In contrast to appellant's directions to the specification and the Figures, the written support and direction for the particular range "for a time ranging from 6 to 10 days" (see claim 7) are not readily apparent from the disclosure as filed.

For example, appellant's reliance on generic disclosure (e.g., administering T cells) and possibly a single or limited species (e.g., testing CD4⁺ T cells with anti-gp39 antibodies under certain conditions in certain Examples for purposes either not claimed or not commensurate with the claimed methods) does not provide sufficient direction and guidance to the claimed methods as currently claimed.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

It is noted that entitlement to a filing date does not extend to subject matter, which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

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The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations", as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 4-7, 10-11 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Noelle et al. (U.S. Patent No. 5,876,718) in view of the art known use of irradiating antigen presenting cells at the time the invention was made, as evidenced by Rooney et al. (U.S. Patent No. 5,962,318) and in view of the art known culturing of donor T cells for treatments over varying lengths of time, as evidenced by Riddell et al. (J. Immunol. Methods 128: 189-201) and monitoring the induction of T cell non-responsiveness ex vivo, as taught by Sykes et al. (U.S. Patent No. 6,006,752) essentially for the reasons of record and further in view of Ochoa et al. (U.S. Patent No. 5,725,855) and Knulst et al. (Eur. J. Immunol. 23: 299-302, 1993) for the reasons of record.

Noelle et al. teach inducing T cell non-responsiveness to desired alloantigens with gp39 antagonists, including the use of anti-gp39 antibodies (i.e. anti-CD40L antibodies) (gp39 Antagonists on columns 5-9) and antigen presenting cells, including bone marrow and peripheral bloods cells (Cells of Induction of Antigen-Specific Tolerance on columns 9-11), for transplantation, including bone marrow transplantation, including reliance upon in vitro / ex vivo manipulations of cells prior to transfer to the transplant recipient (Administration of Cells and gp39 Antagonists and Uses of the Methods of the Invention on columns 9-13) (see entire document, including Detailed Description of the Invention).

Although Noelle et al. does not mention mixed lymphocyte reaction per se, it would have readily apparent to the one of ordinary skill in the art at the time the invention was made that a mixed lymphocyte reaction was accomplished by carrying out the above-mentioned procedures.

Transplantation, including bone marrow transplantation, is provided to recipients in need of immune reconstitution as a result of disease or disease treatment (e.g., see Summary of the Invention on columns 2-4; Administration of Cells and gp39 Antagonists and Uses of the Methods of the Invention on columns 9-13 and Examples).

While Noelle et al. teaches the reactivity of anti-gp39 antibodies on T cells, including CD4⁺ T cells, and teaches the isolation and ex vivo treatment of bone marrow cells (see Examples), Noelle et al. does not teach explicitly the purification and testing of isolated CD4⁺ T cells in a mixed lymphocyte reaction (MLR) under the conditions claimed per se.

Although Noelle et al. is silent about the particular time ranges set recited in the instant claims 6-7 per se, one of ordinary skill would have immediately envisaged at the time the invention was made that the culture of donor T cells would have fallen into such ranges (e.g. 1, 3, 5 days), as known typical days of culturing T cells at the time the invention was made, including the Examples on columns 14-24 set forth in Noelle et al.

In addition, it is noted that Noelle et al. teach that CD4⁺ T cells are required for the induction of cytotoxic T lymphocyte (CTL) formation (e.g. see column 23, paragraph 1) and that anti-gp39 antibodies may induce allospecific tolerance in both the CD4⁺ and CD8⁺ T cell compartments of the immune system, which, in turn would be beneficial in therapeutic interventions when considering transplant immunology and immunotherapy (e.g. see column 24, paragraph 1). Here in the Examples, anti-gp39 antibodies were tested on the ability to block various T cell responses, including MLR subsequent to the in vivo administration of anti-gp39 antibodies as well as the generation of CTL responses to allogeneic cells (e.g. see Examples 1-5).

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It is noted that Noelle et al. teach manipulating Cells for the Induction of Antigen-Specific Tolerance, including antigen presenting cells and T cells, as well as isolation techniques known in the art (see columns 9-11, including column 10, paragraph 2).

In addition, antigen-presenting cells for a variety of immunological processes were routinely irradiated at the time the invention was made to alleviate the activity of other cell types including T cells,

given that antigen presentation was still provided, as evidenced by Rooney et al. (e.g. see columns 14-15, overlapping paragraph and Examples 1-3 in columns 20-36).

Although Noelle et al. does not explicitly disclose monitoring or assaying ex vivo donor T cell tolerance or non-responsiveness as a separate method step, including measuring IL-2; Noelle et al. does clearly teach methods to tolerize T cells in vitro with a gp39 antagonist to affect contact dependent helper effector function (e.g. column 6, paragraph 5, column 11, paragraph 1 and column 13, paragraph 3) and the Examples do exemplify various assays to monitor the induction of T cell tolerance (See Examples on columns 29).

Sykes et al. teach determining the ability of a treated T cell to release a cytokine such as IL-2 to determined the effect of an immunosuppressive drug (see entire document, particularly, column 10, paragraphs 5-6)

With respect to standard procedures of manipulating lymphocytes populations of interest, including ex vivo manipulation of T cells of interest, including CD4⁺ T cells (the target of gp39-/CD40L-specific modulation, as taught by the co-inventor Noelle.) at the time the invention was made.

Rooney et al. teach that the effector cells can be helper CD4⁺ T cells as well as cytotoxic CD8⁺ T cells, which, in turn, can be administered for cellular immunotherapy (e.g. see column 6, paragraph 2).

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Ochoa et al. teach the manipulation of immune cell subsets, including CD4⁺ T cells as well as CD8⁺ T cells ex vivo prior to administration in various therapeutic regimens (see entire document, including Summary of the Invention, Detailed Description of the Invention, including Positive Selection of Cell Subsets on columns 16 –19).

Riddell et al. teach cloning and expanding human antigen-specific T cells, including CD4⁺ T cells as well as CD8⁺ T cells ex vivo prior to administration in various therapeutic regimens (see entire document, including Summary of the Invention and Discussion).

Knulst et al. teach the principal role of CD4⁺ T cells in GVHD and the advantages of treating or inhibiting said CD4⁺ T cells in decreasing morbidity and increasing survival of GHHD patients (see entire document, including Abstract and Discussion).

Sykes et al. also teach that putative immunosuppressive agents and useful concentrations can be prescreened by in vitro or in vivo tests / assays, including those for transplantation (e.g. see column 11, paragraph 1).

With respect to irradiating antigen-presenting cells for ex vivo stimulation, it has been noted that the Examples (e.g., see Example 2 on column 14) of Noelle et al. do provide for such teachings of irradiating antigen-presenting cells for ex vivo stimulation as well as Detailed Description of the Invention of Rooney et al. (e.g. see Antigen Presenting Cells Dendritic Cells and Inducing CTLs for Immunotherapy on columns 12-20).

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Therefore, the prior art provide sufficient direction and motivation to induce antigen-specific non-responsiveness in CD4⁺ T cells, given the use of said CD4⁺ T cells in various therapeutic regimens employing CD4⁺ T cells, and wherein the ordinary artisan would have been motivated to induce such antigen-specific non-responsiveness to avoid deleterious immune responses in the transplant patient, while maintaining the appropriate immune responses, including in certain instances appropriate CD4⁺ T cell immune responses.

Again, it is noted that anti-gp39 antagonists such as anti-gp39 antibodies targeted CD4⁺ T cells, regulatory cells T cells known to be critical in numerous immune responses, including those deleterious to transplant recipients undergoing transplantation of bone marrow or lymphoid cells at the time the invention was made.

Given the teachings of the references, one of ordinary skill in the art at the time the invention was made would have been motivated to culture donor T cells in vitro under certain conditions and times encompassed by the claimed limitations with a gp39 / CD40 ligand antagonist, such as anti-gp39 antibodies, to induce antigen-specific unresponsiveness in the donor T cells populations prior to transplantation for treating various human conditions and diseases. Given the teachings of Noelle et al. and Sykes et al., one of ordinary skill in the art would have been motivated to monitor the effectiveness of the induction of T cell non-responsiveness or tolerance by treating T cells with the gp39 antagonist anti-gp39 antibodies by monitoring various parameters of T cell function, including monitoring the elaboration of cytokines, including IL-2. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Appellant's arguments in conjunction with various legal citations in the Brief on appeal have been fully considered but have not been found persuasive essentially for the reasons of record.

In the interest of convenience, the Sections set forth herein follow the Brief on Appeal.

A. Rejection under 35 U.S.C. § 112, first paragraph,
Written Description / New Matter.

Appellant's arguments and the examiner's rebuttal are essentially those addressed above in the rejection under 35 USC 112, first paragraph, written description / new matter of record.

Appellant relies upon the Examples that explain to those skilled in the art meaning of the terms "purifying CD4⁺ T cell from donor tissue" and "purified donor CD4⁺ T cells/T-cell tolerance" as these terms are used in Steps (iii)-(vi) recited in Claim 1.

Appellant relies mainly on the Examples, which describe "highly purified CD4⁺ lymph node T cells from C.H2^{bm12}" (see Example 1 on page 10 of the instant specification), which provide observations concerning the hyporesponsiveness of isolated CD4⁺ T cells that were exposed to anti-gp39 antibodies in testing the efficacy of anti-gp39 antibodies on those gp39-expressing CD4⁺ T cells or "testing donor T cells (versus purified CD4⁺ T cells) whether they elicit an anti-host allo- / xeno- response, whether such cells remain viable and other elicit normal T cell activity after treatment, e.g. IL-2 responses" (see page 9, paragraph 1 of the instant specification).

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However, the instant methods are not directed to testing the ability of anti-gp39 antibodies to inhibit murine lymph node CD4⁺ T cells in certain experimental situations, as disclosed in the specification as-filed.

Rather, the instant methods are directed towards methods of inducing T cell tolerance or non-responsiveness (versus hyporesponsiveness in instant Examples) by purifying CD4⁺ T cell from donor tissue" (versus describe "highly purified CD4⁺ lymph node T cells from C.H2^{bm12} " and purified donor CD4⁺ T cells/T-cell tolerance" as these terms are used in Steps (iii)-(vi) recited in Claim 1 (versus hyporesponsiveness, testing T cell activity described in instant Examples) and administering purified CD4⁺ T cells to a recipient in need of transplantation.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith, 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Also, it appears that this "limitation" has been added to conveying a critical limitation, not clearly defined in the specification as-filed and was added in an attempt to avoid or alter prior art rejections.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claim 6

As indicated above, the previous rejection under 35 USC 112, first paragraph, written description / new matter with respect to the recitation of "for a time ranging from about 5 to 30 days" recited in claim 6 has been withdrawn in view of the disclosure on page 8, paragraph 4 of the instant specification.

Claim 7

Appellant, in conjunction with Vas-Cath, Ralston Purina and Eiselstein, asserts that there is no per se rule that ranges in claims must correspond exactly with those disclosed in the specification and that the issue is whether one skilled in the art could derive the claimed range from the disclosure as filed relies upon whether one skilled in the art could derive the claimed ranges.

In turn, appellant submits that one skilled in the art could derive the claimed ranges "for a time ranging from 6 to 10 days" from the information disclosed in the specification, as the claimed ranges falls within the range of cell culture maintenance times described in the specification.

In contrast to appellant's directions to the specification, the claimed range "for a time ranging from 6 to 10 days" (see Claim 7) is not readily apparent from the disclosure as filed.

For example, applicant's reliance on generic disclosure (e.g., administering T cells) and possibly a single or limited species (e.g., testing CD4⁺ T cells with anti-gp39 antibodies) does not provide sufficient direction and guidance to the claimed methods as currently claimed.

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The Ralston Purina opinion itself states that written description cases must be decided on a case-by-case basis. See Ralston Purina Co. v. Far-Mar-Co, Inc., 227 USPQ 177 (Fed.Cir. 1985). In finding satisfaction of that requirement, it distinguishes a number of cases in which the requirement was not met "due to a number of different factors." See *id.*

Because of the fact-sensitive nature of the written description inquiry, the Court has often warned against misapplication of precedents in this area. See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) (citing In re Driscoll, 562 F.2d 1245, 1250, 195 USPQ 434 (CCPA 1977)).

In this case, this case-by-case analysis leads to the lack of sufficient written support for the newly added "limitations" and, in turn, to the lack of compliance with the written description requirement.

Given appellant's position, appellant may simply pick and choose any time or any range of times falling within the time span of 1 – 30 days, based upon the disclosure on page 8, paragraph 4 of the instant specification.

For example, given appellant's position, appellant can simply choose a time such as 17 days or a range of 7.5 – 11.5 days, as appellant should so choose.

Also, it is not clear whether the newly added limitations are conveying critical limitations not defined in the specification as-filed or were added in an attempt to avoid or alter prior art rejections.

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A showing of possession of various broad ranges encompassing “a time ranging from 6 to 10 days” (but not describing “day 6”) does not satisfy the statutory mandate that “[t]he specification shall contain a written description of the invention,” and that requirement is not met if, despite a showing of possession, *the specification does not adequately describe the claimed invention.*

However, such a showing of possession of various ranges encompassing “a time ranging from 6 to 10 days” does not cure the lack of a written description in the specification, as required by statute.

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and change the scope of the instant disclosure as-filed.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. See Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Appellant’s arguments have not been found persuasive.

B. Rejection under 35 U.S.C. § 103(a).

Appellant’s arguments that the rejection of record has not established any one of the criteria of obviousness, let alone all of the basic criteria of obviousness, have been fully considered but have not been found convincing essentially for the reasons of record.

(1) Rebuttal: The examiner has failed to cite references that either alone or in combination teach all of the claims 1, 2, 4-11 and 13.

Appellant's arguments and the examiner's rebuttal are essentially the same of record and that addressed herein.

Appellant continues to argue that the instant claims, specifically the steps recited in Claim 1, Steps (i)-(v), are unobvious over the combination of references, since they do not teach or suggest all the limitations of the presently claimed invention, particularly (i) "purifying CD4⁺ T cells from donor tissue" and (ii) irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T cells".

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This, appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to appellant's continued arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

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Appellant focuses on the explicit lack of teaching that the donor T cell must be purified CD4⁺ T cells or that the antigen-presenting cells are first irradiated in the primary Noelle et al. prior art reference, and

ignores the obviousness of these features as simply well known, standard and common applications of isolating cells of interest, including the regulatory CD4⁺ T cells targeted by the gp39 antagonists of the instant methods, and of employing well known or common alternatives in treating antigen-presenting for the induction of antigen-specific tolerance / non-responsiveness, both clearly taught by the co-inventor Noelle et al. prior art reference at the time the invention was made.

Appellant labels the basic procedures of isolating T cells of interest and irradiating antigen-presenting cells (or alloantigen-bearing cells) as crucial aspects of the claimed invention, yet ignores or mischaracterizes standard procedures practiced for decades by the person of ordinary skill in the art at the time the invention was made, whether one considers the field of immunology or adoptive immunotherapy.

As any procedure of isolating a cell or molecule of interest is concerned, isolating cells for treatment or adoptive therapy increases the signal-to-noise ratio of how the cells are treated (e.g., by a gp39 antagonist) or how the cells are administered (e.g., adoptive immunotherapy). Also, working with isolated cells or molecules limits the difficulties with or interference by other cells or molecules, thereby increasing sensitivity, resolution, or impact of the isolated cells or molecules when employed in an assay or method of interest.

Appellant's arguments have not been found persuasive and addressed herein.

(a) Rebuttal: Claim 1, Step (i): "purifying CD4⁺ T cells from donor tissue"

Appellant asserts that the claim limitation of "purifying CD4⁺ T cells from donor tissue" is not disclosed or suggested by any of the cited references either alone or in combination.

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Appellant relies upon the instant Examples alone for the support of this limitation and submits that the use of purified CD4⁺ T cells are important because the products of Example 1 contributed to the results in the other Examples.

However, it is unclear how appellant's reliance on these instant Examples of testing T cell reactivity after the exposure to the gp39 antagonists anti-gp39 antibodies in murine experimental models renders isolating cells of interest by standard and well known and practiced techniques by the ordinary artisan unobvious at the time the invention was made.

In contrast to previous assertions by appellant that laid the groundwork for the current arguments, it was pointed out that Noelle et al. was not limited to in vivo administration of anti-gp39 antibodies, which resulted in the addition of ex vivo claim limitations and the subject of this appeal.

For example, column 11, paragraph, column 11, paragraph 1 of the Noelle et al. discloses that:

"In a case where the cells to be administered are bone marrow cells, wherein inhibition of GVHD is desired, donor T cells in the bone marrow can be tolerized before transfer to the recipient host by incubating the donor bone marrow with B cells from the host and a gp39 antagonist in vitro."

Clearly, the teachings of co-inventor Noelle et al. were all directed toward interfering contact-dependent T cell helper effector functions by targeting gp39 (i.e., CD40 ligand, CD40L) (see entire document, including Summary of the Invention, Detailed Description of the Invention), wherein gp39 (i.e., CD40 ligand, CD40L) is expressed on activated CD4⁺ T helper cells (e.g., see column 2, paragraph 2).

Note that the Background of the Invention on pages 1-3 of the instant specification is the same Background of the Invention of the prior art Noelle et al.

Therefore the ordinary artisan, including co-inventor Noelle, was aware of the issues and procedures of inducing antigen-specific T cell activation and clonal expansion or antigen-specific nonresponsiveness, including the importance of gp39/CD40L-expressing regulatory helper T cells, at the time the invention was made.

The instant methods are drawn to interfering with the same gp39/CD40L on the same regulatory CD4⁺ T helper cells ex vivo to achieve the same therapeutic endpoints to achieve antigen-specific tolerance or non-responsiveness for the same patient populations, as clearly taught by Noelle et al. (e.g., see Summary of the Invention, Detailed Description of the Invention).

The prior art Noelle et al. is clearly directed towards contacting the same targeted gp39/CD40L expressing T cell, which mediates contact dependent helper effector cell, as appellant's claimed methods.

While Noelle et al. may not have explicitly disclosed isolating the targeted gp39/CD40L expressing T cell under in vitro conditions,

the ordinary artisan would have immediately envisaged or would have readily understood that "methods of the prior art used to tolerize a T cell to an antigen in vitro by contacting the T cell in vitro with a cell which present antigen to the T cell together with an antagonist of a receptor expressed on the T cell which mediates contact helper effector function (e.g., see column 6, lines 50-62 of Noelle et al.) was directed at tolerizing gp39/CD40L expressing T cells, which mediates contact dependent helper effector cells, namely targeting the same regulatory CD4⁺ T helper cells ex vivo to achieve the same therapeutic endpoints to achieve the same antigen-specific tolerance or non-responsiveness for the same patient populations, as encompassed by the instant methods.

In response to appellant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. See In re Nomiya, 184 USPQ 607 (CCPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. See In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. See In re Bozek, 163 USPQ 545 (CCPA 1969).

Contrary to appellant's assertions, isolating and manipulating the cells of interest, in this case isolating gp39/CD40L expressing T cells, was well within the knowledge and common sense of the ordinary artisan at the time the invention was made.

Noelle et al. was targeting gp39/CD40L expressing T cells both ex vivo and in vivo methods for the induction of inducing antigen-specific tolerance or nonresponsiveness.

In contrast to appellant's narrow reading of the prior art,

Noelle et al. was not targeting cells that do not express gp39/CD40L or was not trying to induce the expansion or stimulation of immune responses, as implicated by appellant's reading of the secondary references.

Noelle et al. teach manipulating Cells for the Induction of Antigen-Specific Tolerance, including antigen presenting cells and T cells, as well as isolation techniques known in the art (see columns 9-11, including column 10, paragraph 2).

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Here, appellant argues that the secondary references of Rooney, Riddell, Sykes and Ochoa are silent on "purifying CD4⁺ T cells from donor tissue",

but ignores that Noelle et al. has already provided the teachings to target CD4⁺ T helper cells in the ex vivo manipulation to induce tolerance or antigen-specific unresponsiveness.

Appellant also argues that the secondary references such as Rooney et al. are drawn to stimulating immune responses to antigens of interest in adoptive immunotherapeutic regimens.

Again, the secondary references of Rooney, Riddell, Sykes and Ochoa have been provided simply to address some of the basic and common principles and practices of cell culture and manipulation in the art at the time the invention was made at least in response to previous arguments apparently still maintained by appellant concerning the unobviousness of isolating cells (or irradiating cells, discussed in the next Section or length of culture or assays, not argued in Brief on appeal) by the ordinary artisan at the time the invention was made.

Again, whether the endpoints of using T cells in patient populations may be different as cited in the prior art references,

the secondary references are consistent with the teachings of Noelle et al. in the manipulation, growth and expansion of T cells and antigen-presenting cells in culture for therapeutic use known and practiced by the ordinary artisan at the time the invention was made.

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To limit the secondary references to modes of stimulating lymphocytes of interest for purposes other than that taught by Noelle et al. as appellant suggests

simply ignores the purposes and general principles taught by the prior art teachings or what they would have suggested to the ordinary artisan at the time the invention was made,

In particular, appellant arguments fail to adequately address the primary reference Noelle et al., which teaches essentially the same invention as currently claimed; other than focusing on some limitations drawn to standard practices in ex vivo manipulation of cells for adoptive immunotherapy that have added during prosecution to avoid, in part, anticipatory prior art by Noelle et al.

Isolating and manipulating cells of interest were general and common principles applicable to the ordinary artisan in the field of immunology at the time the invention was made and dates back at least to the 1960's.

There is no objective evidence that would supports appellant's assertions that the secondary references lack of teaching "purifying CD4⁺ T cells from donor tissue" for the methods described by the primary reference Noelle et al. would suggest

that the ordinary artisan would not have recognized that the methods of Noelle et al. were drawn to target CD4⁺ T helper cells in the ex vivo manipulation to induce tolerance or antigen-specific unresponsiveness and, in turn,

that the ordinary artisan would not have isolated and manipulated the targeted cell of interest, as commonly practiced at the time the invention was made, as implicitly taught by Noelle et al. (See above) and exemplified in various circumstances as evidenced by the secondary references of Rooney, Riddell, Sykes and Ochoa.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

Appellant has not contradicted the ability, desirability or standard practices by the ordinary artisan to isolate and manipulate T cells of interest by the ordinary artisan at the time the invention was made.

Even the instant specification does not describe methods of purifying CD4⁺ T helper cells, thereby in a sense, acknowledging these well known principles and procedures by the ordinary artisan at the time the invention was made.

For example, the only time the word “purifying” is indicated in the specification as-filed is in the context of Example 1 and the description of “highly purified CD4⁺ lymph node T cells” on page 10 of the instant specification.

Given the desired endpoint of nonresponsiveness, the ordinary artisan would have expected to culture the donor T cells, including the regulatory CD4⁺ T cells, antigen presenting cells with gp39 antagonists for various times, including those encompassed by the claimed invention to achieve the desired endpoint.

Appellant's arguments have not been found persuasive.

(b) Rebuttal: Claim 1, Step (ii): “irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T cells”

Appellant asserts that the claim limitation of “irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T cells” is not taught or suggested by any of the cited references either alone or in combination.

Appellant asserts that the co-inventor Noelle et al. does not teach or suggest the use of irradiation to deplete T cell from a population of alloantigen-bearing cells and that Noelle et al., merely suggest that T cells can be depleted by anti-T cell antibody and not by irradiation.

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While appellant acknowledges that Noelle et al. does teach that T cells can be depleted by anti-T cell antibody,

appellant does not acknowledge the art known and practiced equivalents of preparing antigen-presenting cells at the time the invention was made.

In addition to a narrow reading of the prior art Noelle et al. by appellant, appellant ignores the use of irradiated antigen-presenting cells (e.g., irradiated DBA/2 spleen cells) by the co-inventor Noelle et al. in the prior art Example 2 on the Induction of T cell Tolerance to Allogeneic Cells (see Example 2 on column 14 of Noelle et al.).

It is further noted that Noelle et al. employed mitomycin C as an alternative method to prepare antigen-presenting cells in testing Secondary CTL Responses in Example 3 (see columns 14-16, particularly, column 16, lines 1-6 of Noelle et al.), which also would have suggested that alternative methods of preparing antigen-presenting cells were well known and common practices at the time the invention was made by the ordinary artisan.

Appellant acknowledges that Rooney discloses that general irradiation of alloantigen-bearing cells to select for antigen-specific effector cells, including T cells, such that the irradiation prevents proliferation of alloantigen-bearing cells (e.g., see column 15, lines 2-5 of Rooney).

Appellant's assertions that Rooney's teaching of irradiation to deplete alloantigen-bearing cells, not recipient T cells is simply ignoring what the prior art would have suggested to one of ordinary skill in the art at the time the invention was made.

A reference is not limited to the disclosure of specific working examples. See In re Mills, 176, USPQ 196, 198 (CCPA 1972).

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Appellant is reminded that “irradiating alloantigen-bearing cells obtained from recipient T cells” is for the purpose of preventing proliferation of alloantigen-bearing cells, the same purpose as was well known and commonly practiced by the ordinary artisan at the invention was made in irradiating cells of interest, including antigen-presenting cells, as evidenced by Rooney and acknowledged by appellant.

Appellant has not distinguished “irradiating alloantigen-bearing cells obtained from recipient T cells” known and practiced by the ordinary artisan at the time the invention was made from that claimed,

other than the lack of explicit statements in the prior art that the use of irradiation of alloantigen-bearing cells has the additional property of depleting T cells.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure nor in purposes when compared to the prior art.

For example, it is further noted that the recitation of “to deplete recipient T cells” simply recites a purpose of “irradiating alloantigen bearing cells” in the context of methods of inducing antigen-specific tolerance or nonresponsiveness,

wherein “irradiating alloantigen-bearing cells” does not necessarily depend on the prior art explicit disclosure that the property of irradiating as one in which “irradiation depletes recipient T cells” for completeness.

Rather, preparing antigen-presenting cells by various means, including “irradiation”, in the context of the prior art methods and ingredients to accomplish said methods of inducing antigen-specific tolerance or unresponsiveness, satisfy the claimed limitation of “to deplete recipient T cells” either as an intrinsic property of “irradiation” or a property of intended use of employing the same procedures (e.g., “irradiation”) with the same “alloantigen-bearing cells” or “antigen-presenting cells” to accomplish the same endpoints.

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Again, Noelle et al. teach a variety of antigen-presenting cells, including allogeneic cells or B cells from the host (i.e., recipient) (e.g., see Cells of Induction of Antigen-specific Tolerance on columns 9-13 of Noelle et al.) that read on the claimed limitation of “irradiating alloantigen-bearing cells”.

To suggest that “irradiating antigen-presenting cells” in the prior art somehow does not render the claimed limitation of “irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T cells” runs counter to the basic principles of irradiating antigen-presenting cells in such culture systems and to the basic principles of inducing antigen-specific T cells responses,

whether the purpose was to enhance or to tolerize such antigen-specific T cells responses with the use of irradiated antigen-presenting cells.

Irradiating “alloantigen-bearing cells” or “antigen-presenting cells” having the property of “depleting recipient T cells” would have been readily apparent as routine practice to the ordinary artisan at the time the invention was made, including the prior art teachings of co-inventor Noelle in the prior art or in the current claimed methods.

For example, as pointed out previously and in contrast to applicant’s assertions, antigen presenting cells for a variety of immunological processes were routinely irradiated at the time the invention was made to alleviate the activity of other cell types including T cells given that antigen presentation was still provided, as evidenced by Rooney et al. (e.g. see columns 14-15, overlapping paragraph and Examples 1-3 in columns 20-36).

Again, it is noted that Noelle et al. teach depleting antigen presenting cells of T cells (see column 10, paragraph 2).

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While appellant argues that Rooney et al. is drawn to stimulating immune responses to antigens of interest in adoptive immunotherapeutic regimens,

it has been pointed out that Rooney et al. along with the other secondary references was provided simply to address some of the basic principles and practices of cell culture and manipulation in the art at the time the invention was made, and perhaps for the past 20 years at least.

Again, whether the endpoints of using T cells in patient populations may be different in the secondary prior art references,

Rooney et al. is consistent with the teachings of Noelle et al. in the growth and expansion of T cells in culture for therapeutic use and the manipulation of antigen presenting cells.

Appellant appears to focus upon the recitation of intended use of irradiation "to deplete recipient T cells",

while ignoring that the claims are drawn to irradiating alloantigen-bearing cells, namely the antigen-presenting cells of the ex vivo manipulation of Cells for Induction of Antigen-specific Tolerance and Administration of Cells and gp39 Antagonists (see columns 9-13 of Noelle et al.), wherein the prior art provides for the obviousness of irradiating the same alloantigen-bearing cells, namely the antigen-presenting cells as recited in the instant claims, wherein irradiation was employed to prevent proliferation of cells and to alleviate the activity of other cell types.

In a similar fashion, appellant appears to dismiss the secondary references Riddell, Sykes, Knulst and Ochoa by indicating that they are silent on the use of irradiation to select subpopulations of cells to the exclusion of recipient T cells or to deplete only CD4⁺ T cells.

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However, appellant does not appear to accept the well known and standard use of irradiation in the ex vivo manipulation of lymphocyte or leukocyte populations and its applicability to the basic teachings of the co-inventor Noelle et al. or already acknowledged by appellant, wherein appellant at the same time is attempting to dismiss the secondary references as distinct from the claimed invention.

It is noted that that appellant's asserted "use of irradiation to select subpopulations of cells to the exclusion of recipient T cells" or "to deplete only CD4⁺ T cells" are limitations not claimed, nor change the prior art teaching irradiating the same alloantigen-bearing cells or antigen-presenting cells with the same irradiation to achieve the same goals of inhibiting.

Appellant has not contradicted the ability of irradiation of antigen-presenting cells or alloantigen-bearing cells, which appellant admits was a well known practice to prevent the proliferation of non-specific cells, to deplete T cells.

Appellant has not contradicted nor distinguished this decades-old practice of irradiating antigen-presenting cells or alloantigen-bearing cells between the prior art and the instant methods.

In contrast to appellant's assertions concerning the prior art teaching away by focusing on the secondary references, the following is noted.

Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. See In re Susi USPQ 423 (CCPA 1971).

In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art.

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here again, in contrast to appellant's assertions of teaching away by the prior art Ochoa reference because this reference is directed towards a different outcome than that currently claimed,

the combined teachings, including the secondary references, do not raise discouragement nor skepticism in the prior art for the common and standard practice of irradiating antigen-presenting cells or alloantigen-bearing cells in methods to manipulate antigen-specific responses by T cells, whether the intent was to induce expansion of antigen-specific T cells to induce nonresponsiveness of antigen-specific T cells at the time the invention was made.

Appellant's arguments have not been found persuasive.

(c) Rebuttal: Claim 1, Steps (iii)-(v).

Given that appellant's arguments have not been convincing with respect to steps (i) and/or(ii) above, appellant's reliance on the non-obviousness of steps (i) and/or(ii) as it reads on steps (iii)-(iv) is similarly found unconvincing for the reasons of record and addressed herein the rejection of record and the rebuttal to arguments.

In contrast to appellant's arguments the use of purified CD4⁺ T cells and irradiated antigen-presenting cells were obvious modifications in the ex vivo manipulation of Cells for Induction of Antigen-specific Tolerance and Administration of Cells and gp39 Antagonists (see columns 9-13 of Noelle et al.).

Appellant's arguments have not been found persuasive.

(2) Rebuttal: The examiner has failed to cite references or general knowledge that would suggest or motivate one having ordinary skill in the art to modify or combine the reference teachings to arrive at the invention claimed in claims 1, 2, 4-11 and 13.

Appellant's arguments in conjunction with various legal citations have been fully considered but have not been found convincing essentially for the reasons of record.

Appellant asserts that the correct standard for combining prior art references requires that each reference must provide some suggestion of motivation to combine those features identified by the examiner to arrive at the claimed invention.

Appellant asserts that the result achieved by the claimed invention is induced immunological tolerance – not enhanced immunological response and asserts that the cited references, namely the secondary references, would have led the ordinary artisan to an opposite concept from the claimed induced immunological tolerance.

Again, appellant simply ignores the primary reference by co-inventor Noelle, where the prior art methods are the same or nearly the same in every aspect except for well known and standard methods of isolating the same CD4⁺ T cells targeted by the same gp39 antagonist and of irradiating antigen-presenting cells as broadly recited in the instant claimed invention.

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In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. See In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. See In re Bozek, 163 USPQ 545 (CCPA 1969).

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

Noelle et al. teach inducing T cell non-responsiveness to desired alloantigens with gp39 antagonists, including the use of anti-gp39 antibodies (i.e. anti-CD40L antibodies) (gp39 Antagonists) and antigen presenting cells, including bone marrow and peripheral bloods cells (Cells of Induction of Antigen-Specific Tolerance), for transplantation, including bone marrow transplantation, including before transfer to the transplant recipient in vitro (Administration of Cells and gp39 Antagonists) (see entire document, including Detailed Description of the Invention).

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A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here, in contrast to applicant's assertions, the prior art primary reference of Noelle et al. is clearly drawn to the same or nearly the same methods to achieve the same therapeutic endpoints as the current claimed methods. The secondary references simply filled in well -practiced and established methods of manipulating and testing immune cells, particularly T cell – antigen presenting cell interactions. There is no discouragement, nor skepticism in the prior art for the ex vivo manipulation of donor and recipient cell populations to achieve antigen specific non-responsiveness in transplantation regimens at the time the invention was made.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This appellant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

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Here again, in contrast to appellant's assertions of teaching away by the prior art references because the secondary references describe different outcomes than that currently claimed,

the combined teachings, including the secondary references, do not raise discouragement nor skepticism in the prior art for the common and standard practices employed in ex vivo methods to manipulate antigen-specific responses by T cells, whether the intent was to induce expansion of antigen-specific T cells to induce nonresponsiveness of antigen-specific T cells at the time the invention was made.

In this case, the teachings of the primary reference Noelle et al. pertaining to the difficulties in inducing antigen-specific non-responsiveness by manipulating donor and host immune cell populations as well as methods to accomplish such goals coupled with the teachings of secondary references in providing for well-established and common culture conditions and manipulation in generating specific cell interactions and endpoints would have led the ordinary artisan to solve the same a well known problem in the art by combining the references. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

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Given the teachings of the references, one of ordinary skill in the art at the time the invention was made would have been motivated to culture donor T cells ex vivo under certain conditions and times encompassed by the claimed limitations with a gp39 / CD40 ligand antagonist such as anti-gp39 antibodies to induce antigen-specific unresponsiveness in the donor T cells populations prior to transplantation for treating various human conditions and diseases.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Appellant's arguments have not been found persuasive.

(3) Rebuttal: The examiner has failed to cite references that give rise to a reasonable expectation of success in achieving the invention claimed in claims 1, 2, 4-11 and 13.

As pointed out above repeatedly, appellant's assertions that well known practices of isolating or purifying and manipulating cells of interest, including CD4⁺ T cells, as well as irradiating antigen-presenting cells or alloantigen-bearing cells; by the ordinary artisan at the time the invention was made simply ignores such well known practices these standard practices and mischaracterize the prior art references, particularly the secondary references.

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Perhaps more noteworthy is appellant's ignoring the basic teachings by the co-inventor Noelle et al. to manipulate Cells for Induction of Antigen-specific Tolerance and antibodies to induce antigen-specific unresponsiveness in the donor T cells populations prior to transplantation for treating various human conditions and diseases by the Administration of Cells and gp39 Antagonists (see columns 9-13 of Noelle et al.).

Also, appellant takes the curious position of indicating that co-inventor Noelle et al. teaching in the prior art was highly unpredictable,

although the co-inventor Noelle et al. clearly teaches methods of inducing antigen-specific tolerance or nonresponsiveness essentially by the same or nearly the same method steps, including ex vivo method steps, and ingredients for the treatment of the same or nearly the same patient populations at the time the invention was made.

In addition in reviewing the prior art Summary of the Invention and Detailed Description of the invention by Noelle et al., appellant is also invited to note the Claims of the prior art Noelle et al., which are drawn to method of inducing T cell nonresponsiveness.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

Appellant has not provided sufficient objective evidence to counter the prior art teachings as well as Claims of an expectation of success in inducing antigen-specific tolerance or nonresponsiveness via gp39 antagonists, as taught by co-inventor Noelle et al. at the time the invention was made.

Appellant's arguments have not been found convincing of unexpected results in view of the clear motivation and expectation of success in inducing T cell specific non-responsiveness both via ex vivo as well as in vivo manipulations.

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Appellant's arguments have not been found persuasive.

(11) Related Proceedings Appendix.

A copy of the Panel Decision from Pre-Appeal Brief Review dated August 3, 2006 for the instant USSN 09/835,126 as well as the Panel Decision from Pre-Appeal Brief Review dated August 3, 2006 for related USSN 09/951,537 identified in the Related Appeals and Interferences Section of this Examiner's Answer has been provided in the Evidence Appendix of the Appeal Brief, filed October 3, 2006.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,




Phillip Gambel, Ph.D., J.D.

Primary Examiner

Art Unit 1644

January 3, 2007

Conferees:


Christina Chan, SPE

Larry Helms, SPE


LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER